REMARKS

Favorable reconsideration in view of the herewith presented amendment and remarks is respectfully requested.

Claims 4 and 8 are pending in this application. Claims 5 and 11 are cancelled.

Claims 4, 5, 8 and 11 are rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. In particular, the Examiner has pointed out that the limitation "1 μg to 50 mg/human of poly(I):poly(C)" in claims 4 and 5 is not supported by the instant application.

Claim 4 has been amended to recite the limitation "1 μg to 50 mg/man per dose of poly(I) :poly(C)". Support for this amendment can be found on page 8, line 16 in the specification. It is believed this rejection has been overcome and withdrawal of the rejection is requested.

Claim 5 is cancelled. This rejection is believed to be moot.

Claim 8 is dependent upon claim 4. Claim 4 has been amended to recite the limitation "1 μg to 50 mg/man per dose of poly(I):poly(C)", which support can be found on page 8, line 16 in the specification. It is believed this rejection has been overcome and withdrawal of the rejection is requested.

Claim 11 is cancelled. This rejection is believed to be moot.

Claims 4, 5, 8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 has been amended to recite the limitation "1 μg to 50 mg/man per dose of poly(I) : poly(C)". Support for this amendment can be found on page 8, line 16 in the specification. It is believed this rejection has been overcome and withdrawal of the rejection is requested.

Claim 5 is cancelled. This rejection is believed to be moot.

Claim 8 is dependent upon claim 4. Claim 4 has been amended to recite the limitation "1 μg to 50 mg/man per dose of poly(I) : poly(C)", which support can be found on page 8, line 16 in the specification. It is believed this rejection has been overcome and withdrawal of the rejection is requested.

Claim 11 is cancelled. This rejection is believed to be moot.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desmyter et al., YANO 1, Bever et al. in further view of Liaw.

Applicants respectfully traverse these rejections.

The Examiner asserts that Desmyter teaches that interferon and interferon inducers have been studied for treating hepatitis in a patient and chimpanzees. The Examiner further states that Desmyter teaches that the administration of poly(I):poly(C) to the mammals results in direct action of interferon in the liver.

Applicants assert that Desmyter does not teach at all that the administration of poly(I):poly(C) to a mammal can induce the expression or production of interferon chiefly in the liver. The complex of the present invention is accumulated in the liver by 80% and can induce interferon especially in the liver. Since the hepatitis virus increases only in the liver, it is very reasonable to induce interferon chiefly in the liver. If interferon is induced chiefly in the liver, toxicity in organs other than liver could be much less than expected. Further, as admitted by the

Examiner, Desmyter does not specifically teach intravenously, hepatic intra-arterially, or transmucosally administering a complex comprising administering cationic liposome with 1 μg to 50 mg/man of poly(I):poly(C) , which has a mean length within the range of 100 to 500 bp. The dosage of poly(I):poly(C) is much lower than that in Desmyter.

The Examiner is also of the opinion that YANO 1 teaches that poly(I):poly(C) is a substance having interferon induction action and can be used for treating viral infections. The Examiner asserts that YANO 1 teaches that when the chain length is limited to certain ranges, the resulting substance exhibit desired physiological activity with markedly less toxicity. In particular, the Examiner asserts that YANO 1 teaches that the fact that the control of molecular size of nucleic acid polymer within a specified range is the primarily important factor for remarkable reduction of toxicity of poly(I):poly(C) and the preferred molecular size for using poly(I):poly(C) is from 100 to 600 base numbers. Further, the Examiner asserts that YANO 1 teaches that the dsRNA can be delivered to an individual using different routes of delivery, including subcutaneous, intramuscular, or intravenous.

Applicants disagree with the Examiner. YANO 1 teaches that when the chain length of the double stranded nucleic acid derivatives is limited to certain ranges (100 to 600 base numbers, column 11 lines 30-34), the resulting substances exhibit desired physiological activity with markedly less toxicity (column 4 lines 34-39). YANO 1 also teaches that poly(I):poly(C) derivatives, i.e., "mismatched poly(I):poly(C)", exhibited far stronger activity as compared with unmodified normal poly(I):poly(C) according to the present invention, with very low toxicity (column 4, lines 25-30). Therefore, it would not have been obvious whether the teaching for poly(I):poly(C) derivatives could be applied to the case of the unmodified normal

poly(I):poly(C) because it has an activity weaker than that of poly(I):poly(C) derivatives. Far from being weak, 500-600 bp short-chained poly(I):poly(C) can not induce IFN by itself.

The Examiner further asserts that Bever teaches i.v. administration of 100 μg/kg poly(I):poly(C) in humans, wherein the administration of poly(I):poly(C) produced substantial levels of IFN. According to the Examiner, Bever teaches that substantial levels of IFN were produced when poly(I):poly(C) was administered weekly, biweekly and monthly. The Examiner alleges that in view of the levels of IFN produced by administering poly(I):poly(C) to a human taught by the prior art (e.g. Desmyter and Bever), one of ordinary skill in the art would have reasonably expected that poly(I):poly(C) could be used to treat hepatitis in a human with a reasonable expectation of success.

Applicants disagree with the Examiner. Desmyter and Bever use a complex of poly-L-Lysine and carboxymethylcellulose with poly(I):poly(C) (poly ICLC). Poly ICLC is not a complex of a cationic liposome with poly(I):poly(C) in connection with the present invention. Namely, poly-L-Lysine and carboxymethylcellulose do not compose a cationic liposome. The administration of complex of the present invention is entirely different from that of interferon itself, poly(I):poly(C) alone, or poly ICLC in pharmacological action or effect.

The Examiner further states that it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever and Liaw to treat hepatitis C in a human using intravenous or transmucosal administration of a complex comprising a cationic liposome with 1 μg to 50 mg/man of poly(I):poly(C) which has a mean length within the range of 100 to 500 bp; once, every day, every other day, weekly, or bi-weekly and inducing interferon chiefly in the liver in a human. The Examiner also states that prior art teaches that

poly(I):poly(C) can produce enough IFN to treat hepatitis in patients and mammals (page 7 lines 13-17 in the office action).

Applicants disagree with the Examiner. The chain-length of the poly(I):poly(C) is not disclosed in the prior art, and neither is it disclosed if the toxicity of the poly(I):poly(C) is low enough for clinical application. If the average chain length of the poly(I):poly(C) is longer, more IFN-beta could be induced but the toxicity would be higher.

Table 3 shows that the longer the average chain length of poly(I):poly(C) is, the more IFN-beta is induced. That means that the shorter the average chain length of poly(I):poly(C) is, the less IFN-beta is induced. The chain-length of 100-500bp according to the present invention is so short that the IFN inducing activity of poly(I):poly(C) of 100-500bp is expected to be very weak. Also, we have indicated that the poly(I):poly(C) of 500-600bp alone could not induce IFN even at high concentration of 100ng/ml. It would not have been obvious if the present complex containing 100-500bp short-chained poly(I):poly(C) which did not possess IFN-inducing activity by itself, could induce enough IFN for the treatment of human hepatitis.

Claims 4, 5, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desmyter et al., YANO 1, Bever et al. in further view of Liaw, and further in view of YANO 2.

Applicants respectfully traverse these rejections.

Desmyter, YANO 1, Bever, and Liaw do not specifically teach using the complex (2-O-(2-diethylaminoethyl)carbamoyl-1,3,-O-dioleolyglycerol and a phospholipid, e.g. lectithin) in the method, as the Examiner admits in the 7th line to 5th line from the bottom of page 9 in the office action. Further, it would not have been obvious to one of ordinary skill in the art that the present complex containing 100-500 bp short-chained poly(I):poly(C) which does not possess IFN-

inducing activity by itself, could induce enough IFN for the treatment of human hepatitis, even when YANO 2 teaches that using a complex comprising 2-0-(2-diethylaminocethyl) carbamoyl-1,3-0-dioleoylglycerol and a phospholipid, e.g., lecithin, to administer double stranded RNA to an individual reduces toxicity of the double stranded RNA and improves the uptake efficiency of the double stranded RNA into cells ('457, abstract and pages 2-11).

The Examiner is also of an opinion that it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever, and Liaw in further view of YANO 2 to use i.v., hepatic intra-arterial, or transmucosal administration of the complex to treat hepatitis C in a human. The Examiner further asserts that one of ordinary skill in the art would have been motivated to use the administration routes to deliver the complex to treat hepatitis in a human because the prior art teaches that these routes of administration would produce enough IFN to treat hepatitis C in a human and these administration routes were well known to one of ordinary skill in the art for delivering poly(I):poly(C) to a mammal.

Applicants disagree with the Examiner. As discussed above, Desmyter and Bever use poly ICLC, which is not a complex of a cationic liposome with poly(I):poly(C) in connection with the present invention. YANO 1 does no teach if the short-chained poly(I):poly(C) can induce interferon chiefly in the liver in an amount sufficient to treat hepatitis in a human. Desmyter and Bever teach that when poly ICLC was administered to chronic hepatitis B models of chimpanzzees and patients with multiple sclerosis (MS), hepatitis B (HBV)-related antigens in chimpanzees were suppressed and interferon of substantial level was produced in MS patients. However, neither Desmyter nor Bever teaches about the toxicity of poly ICLC.

The present invention teaches that 1 μg-50 mg of poly(I):poly(C) which has a mean length within the range of 100-500 bp in the complex has markedly less toxicity, and at the same

time it can induce a substantive amount of interferon chiefly in the liver enough to treat hepatitis. It would not have been obvious for a person of ordinary skill to get both the induction of interferon chiefly in the liver in an amount sufficient for the treatment of hepatitis and at the same time markedly lower toxicity by administering the complex of the present invention. The present invention is urged patentable over the prior art.

None of the other prior art relied upon by the Examiner remedies the deficiencies noted above in the primary citations.

Reconsideration and withdrawal of all the Examiner's §112 and §103 rejections is respectfully requested.

It is believed that all of the present claims are in condition for allowance. The Examiner is requested to reconsider and withdraw all of the rejections made in the Official Action. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

If the Examiner believes that issues may be resolved by telephone interview, the Examiner is respectfully urged to telephone the undersigned at (212) 801-2134. The undersigned may also be contacted by e-mail at diebnerg@gtlaw.com.

A one month extension of time fee is believed to be necessary. The Commissioner is hereby authorized to charge that fee, and any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 50-1561.

Dated: January 4, 2006

By: Respectfully submitted,

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